REMARKS

Claim 1 has been amended to recite "A kit . . .," to recite "injectable magnesium" and "calcium in oral administration form," and that "the injectable calcium and calcium in oral administration form are separate compositions." Support for these amendments can be found throughout the specification including, for example, page 5, line 15 to page 6, line 1 and page 6, lines 29-37; in the Examples (page 8, line 23 - page 13, line 26); and in original claims 1-3 and 5.

Claim 4 has been amended to recite "A kit . . ." and to recite "injectable calcium," "calcium in oral administration form," and "injectable magnesium." Support for these amendments can be found throughout the specification including, for example, page 5, line 15 to page 6, line 1 and page 6, lines 29-37; in the Examples (page 8, line 23 - page 13, line 26); and in original claims 1-3 and 5.

Claims 5 and 12 have been amended to recite "A kit . . . ." Support for this amendment can be found throughout the specification including, for example, page 5, line 15 to page 6, line 15 and page 6, lines 29-37; in the Examples (page 8, line 23 - page 13, line 26); and in original claims 1-3 and 5.

Claim 6 has be amended to recite the administering of calcium and magnesium by injection and "administering calcium by the oral route as a gluconate, chloride, bromogalactogluconate, gluconolactate or carbonate salt following the treatment with oxaliplatin." Support for these amendments can be found throughout the specification including, for example, page 5, line 15 to page 6, line 15 and page 6, lines 29-37; in the Examples (page 8, line 23 - page 13, line 26); and in original claims 1-3 and 5-8.

Claims 11 and 13-14 have been amended to conform to the amendment of claim 6, from which they depend. Support for

these amendments can be found throughout the specification including, for example, page 5, line 15 to page 6, line 15 and page 6, lines 29-37; in the Examples (page 8, line 23 - page 13, line 26); and in original claims 1-3 and 5-8.

Applicants submit that no new matter has been added via these amendments to the claims.

Interview Summary

Examiners Klinkel and Mehta are thanked for the courtesies extended during telephonic interview conducted with the undersigned on December 8, 2009. In the interview, the undersigned presented a draft set of claim amendments for discussion. Based on the draft claim amendments, the Examiners agreed, if sufficient written description in the specification were present, that "the proposed amendments . . . appeared to overcome all rejections of record." (*See* Interview Summary (Paper No. 20091208) dated December 15, 2009)

The amendments discussed in the interview, have been submitted on the record above. In addition, the support in the specification for the amendments has been clearly identified above. Accordingly, based on the amendments, Applicants submit that all of the outstanding rejections have been met and respectfully request withdrawal of the rejections.

35 U.S.C. § 112, Second Paragraph

Claims 1, 4-5, 12, and 14 have been rejected as indefinite because, in the view of the Examiner, "it is unclear what is meant by the claimed 'combination'. It is unclear whether this claim is directed toward a composition, a kit or a method of treatment." (Paper No. 20090817 at 3.) In addition, the Examiner has alleged that "it is unclear what is meant by the descriptors 'injectable' and 'oral form' with respect to calcium and/or magnesium." (*Id.*)

Claim 1 has been amended to recite "A kit . . . ." In addition, claim 1 has been amended to recite injectable calcium, injectable magnesium, calcium in oral administration form, and that the injectable calcium and calcium in oral administration form are separate compositions. Moreover, the specification clearly sets forth what is meant by the terms "injectable form" and "oral form":

> **[0028]** The expression **injectable form is understood to mean**, for the purposes of the present invention, any liquid form capable of transporting the composition into the human body of a patient, such as for example isotonic solutions.
>
> **[0029]** The expression **oral form is understood to mean** any form suitable for oral administration, in particular tablets, capsules and solutions.

(U.S. Patent Application Publication 2005/0148661.)

In view of these amendments, it is submitted that one of ordinary skill in the art, when reading the instant claims in light of the specification, would readily have recognized the particular area set out and circumscribed by the claims. Accordingly, Applicants submit that the claims fully comply with all of the requirements of 35 U.S.C. § 112. Reconsideration and withdrawal of the rejection are therefore respectfully solicited.

Claims 4-5 have also been rejected as indefinite, because, in the view of the Examiner, there "is insufficient antecedent basis for" the limitation "the calcium" in these claims. (Paper No. 2000817 at 4.) Claim 1 has been amended to recite "injectable calcium" and "calcium in oral administration form." For consistency, claim 4 has also been amended to recite "injectable calcium" and "calcium in oral administration form." Moreover, claim 5 has been amended to delete the recitation of "the calcium."

In view of these amendments, the limitations of claims 4 and 5 find full antecedent basis support in the claim(s) from which they depend. Accordingly, Applicants submit that the claims fully comply with all of the requirements of 35 U.S.C. § 112. Reconsideration and withdrawal of the rejection are therefore respectfully solicited.

Claim 5 has also been rejected as indefinite, because, in the view of the Examiner, there "is insufficient antecedent basis for" the limitation "said injectable magnesium salt" in the claim. (Paper No. 2000817 at 4-5.) Claim 4 has been amended to recite "the injectable magnesium is present in as a sulfate or pidolate salt."

In view of this amendment, the limitation "said injectable magnesium salt" finds full antecedent basis support in claim 4, from which claim 5 depends. Accordingly, Applicants submit that the claim fully complies with all of the requirements of 35 U.S.C. § 112. Reconsideration and withdrawal of the rejection are therefore respectfully solicited.

Claim 12 has been rejected as indefinite, because, in the view of the Examiner, there "is insufficient antecedent basis for" the limitation "said injectable magnesium" in the claim. (Paper No. 2000817 at 5.) Claim 12 has been amended to recite "said injectable magnesium salt." Claim 5 explicitly recites ""said injectable magnesium salt."

In view of this amendment, the limitation "said injectable magnesium salt" finds full antecedent basis support in claim 5 from which claim 12 depends. Accordingly, Applicants submit that the claim fully complies with all of the requirements of 35 U.S.C. § 112. Reconsideration and withdrawal of the rejection are therefore respectfully solicited.

Claim 14 has been rejected as indefinite, because, in the view of the Examiner, it "is unclear which calcium is administered following treatment with oxaliplatin this claim refers to. Claim 6, upon which claim 14 ultimately depends from, requires that calcium and magnesium be administered both before and after treatment with oxaliplatin. Claim 13, upon which claim 14 directly depends recites the administration of calcium by the oral route following treatment with oxaliplatin." (Paper No. 2000817 at 5.)

Claim 6 has been amended to recite "administering calcium by the oral route." For consistency, claim 13 and 14 have both been amended to recite "the calcium administered by the oral route."

In view of these amendments, it is submitted that one of ordinary skill in the art, when reading the claim 14 would readily have recognized the particular area set out and circumscribed by the claims. Accordingly, Applicants submit that the claim fully complies with all of the requirements of 35 U.S.C. § 112. Reconsideration and withdrawal of the rejection are therefore respectfully solicited.

35 U.S.C. § 112, First Paragraph

Claims 6, 11, and 13-14 have been rejected under § 112, first paragraph, as containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors, at the time that the application was filed, had possession of the claimed invention. (Paper No. 20090817 at 5-6.) The Examiner has alleged that there is no support in the specification for the recitation in claims 6 and 13 of "at least 1 g calcium," "at least 1 g of magnesium," and "at least 1 g/day." (*Id.* at 6.) The Examiner has alleged that "the specification provides support for 1 g calcium and 1 g magnesium

(see [0030]) and 1 g/day (see [0031]), but not for any amounts greater or less that these amounts." (*Id.*) Applicants respectfully traverse this rejection.

The specification clearly provides support for the recited phrases. In particular, the specification teaches:

> **[0024]** In an advantageous embodiment of the invention, the products are characterized in that the concentrations of injectable calcium are between 8 and 20 mg/ml and the concentrations of injectable magnesium are between 10 and 20 mg/ml, preferably 15 mg/ml (these concentrations are expressed as calcium ions).
>
> **[0025]** The concentrations of calcium and magnesium salts are chosen so as to allow **intravenous administration of 2 to 3 g/day of said salts during the administration of oxaliplatin**. The calcium concentrations are chosen so as to allow **administration of 1 to 2 g/day per os during the eight days which follow**.

(U.S. Patent Application Publication 2005/0148661.) Accordingly, the specification provides explicit support for at least 1 g calcium, at least 1 g of magnesium, and at least 1g/day.

In view of the foregoing, the specification as filed satisfies the written description requirement and one skilled in the relevant art would readily have recognized that the Applicants were, at the time that the application was filed, in possession of the claimed invention. Accordingly, Applicants submit that the claim fully complies with all of the requirements of 35 U.S.C. § 112. Reconsideration and withdrawal of the rejection are therefore respectfully solicited.

35 U.S.C. § 102

Claims 1 and 4 have been rejected as anticipated by Lainé-Cessac et al., Acute Oxaliplatin Neurotoxicity Dramatically Improved with Intravenous Calcium and Magnesium Salts, Therapie, Vol. 53, p. 183 (1998) ("Lainé-Cessac"). (Paper No. 2000817 at 6.) The Examiner has alleged that teaches

that the anticancer agent oxaliplatin induces neurotoxicity (1st sentence). This neurotoxicity can be dramatically improved by immediately treating patients undergoing oxaliplatin treatment with intravenous calcium gluconate (1 g) and magnesium sulfate (1 g)."

Claim 1 has been amended to recite "A kit . . . comprising: a. oxaliplatin, b. injectable calcium, c. injectable magnesium, and d. calcium in oral administration form, wherein the injectable calcium and calcium in oral administration form are separate compositions." *Lainé-Cessac*, at best, teaches a single injectable form of calcium. Thus, *Lainé-Cessac* does not teach two different forms of calcium. Nor does it teach any calcium in oral administration form.

Anticipation requires "identity of invention." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply,* 33 U.S.P.Q.2d 1496, 1498 (Fed. Cir. 1995). Each and every element recited in a claim must be found in a single prior art reference and arranged as in the claim. *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 221 U.S.P.Q. 481, 485 (Fed. Cir 1984). *Lainé-Cessac* does not teach each and every element of the claimed process as arranged in the claims, as amended. Accordingly, *Lainé-Cessac* is insufficient to support a *prima facie* rejection of the claims for anticipation. Withdrawal of the rejection is respectfully requested.

35 U.S.C. § 103(a)

Claims 5-6 and 11-12 have been rejected under 35 U.S.C. § 103(a) as unpatentable over *Lainé-Cessac*. (Paper No. 2000817 at 8.) In making the rejection, the Examiner has relied on the previous characterization of *Lainé-Cessac*. (*Id.*) The Examiner has acknowledged that *Lainé-Cessac* does not explicitly teach the concentrations of calcium and magnesium recited in claims 5 and 12. (*Id.*) The Examiner has determined

that that it would have been obvious to arrive at the claimed concentrations, because *Lainé-Cessac* teaches 1 g of calcium and 1 g of magnesium via IV and that would require the selection of roughly 150 ml for infusion to produce the claimed concentrations.

As noted above, with regard to the rejection of claims 1 and 4 as anticipated, *Lainé-Cessac* teaches only intravenous administration of calcium and magnesium. Thus, *Lainé-Cessac*, at best, teaches a single injectable form of calcium. *Lainé-Cessac* does not teach two different forms of calcium. Nor does it teach any calcium in oral administration form. The rejection offers nothing to close this gap. Thus, one of skill in the art would have had no rationale to also administer calcium by an oral route, as claimed.

Accordingly, the *Lainé-Cessac* is simply insufficient support a *prima facie* case for the obviousness of the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 13-14 have been rejected under 35 U.S.C. § 103(a) as unpatentable over *Lainé-Cessac* in view of Chazard, U.S. Patent Application 2002/0045632 ("*Chazard*"). (Paper No. 20090817 at 10-11.) In making the rejection, the Examiner has relied on the previous characterization of *Lainé-Cessac*. (*Id.* at 11.) The Patent Office has acknowledged that *Lainé-Cessac* does not teach "the use of an oral calcium formulation nor the administration dosages or schedules." (*Id.*)

To fill the acknowledged gap, the Patent Office has relied on *Chazard* as disclosing "the use of an oral formulation of calcium folinate to potentiate the coadministration of oxaliplatin in order to treat tumors (abstract, paragraph 36)." (*Id.*) The Patent Office then determined that "[i]t would have been obvious . . . to supplement the IV administration of Ca and

Mg before and after treatment with oxaliplatin with at least 1 g/day oral calcium and for 8 days after treatment with oxaliplatin given the combined teachings of the prior art." (*Id.*)

Lainé-Cessac discloses that the acute neurotoxic effects of oxaliplatin administration can be dramatically improved by intravenous administration of calcium gluconate and magnesium sulfate immediately after onset of the neurotoxic effects. *Lainé-Cessac* is silent as to oral administration of calcium.

Chazard discloses "[o]ral dosage form for administration of the combination of tegafur, uracil, folinic acid, and oxaliplatin and method of using the same." (Title (emphasis added).) In fact, *Chazard* is directed specifically to an oral dosage as an improvement upon an injectable form of it compositions:

> It has been observed that 5-fluorouracil can enhance the activity of oxaliplatin. However, because 5-fluorouracil cannot be administered orally, the mode of administration for this combination therapy requires a more invasive form of administration such as by intravenous injection, and therefore typically requires administration by trained medical personnel.
>
> ***It would be an advance*** in the art of treating tumors, especially colorectal cancerous tumors, ***if a therapy could be developed employing a potentiated form of oxaliplatin through the action of 5-fluorouracil in a convenient dosage form for oral administration***.

(¶¶ 0007-0008 (emphasis added).)

Chazard discloses that "5-fluorouracil cannot be administered orally." (¶ 0003.) *Chazard* discloses, however, that "the combination of tegafur and uracil in amounts sufficient to convert tegafur to 5-fluorouracil (preferably a molar ratio of about 1:4) can be administered orally. It was unexpectedly discovered that oral administration of this combination produced sufficient 5-fluorouracil that potentiation

of oxaliplatin would take place despite the inability of 5-fluorouracil itself to be effectively administered orally." (¶ 0015.) In sum, *Chazard* explicitly discloses that oral administration of its compounds is absolutely critical to the invention:

> The ***oral dosage form*** used in the present invention ***provides significant advantages*** over administering the combination by other modes of administration which are more invasive. In the treatment of tumors, a potential ***reduction in the cost of therapy*** because skilled medical personnel are not required to administer the drug and the ***psychological benefits afforded a patient*** by taking an oral medication provide significant benefits for patient care.

(¶ 0016 (emphasis).)

Claim 6, from which claim 13 and 14 depend, has been amended to recite "administering calcium by the oral route as a gluconate, chloride, bromogalactogluconate, gluconolactate or carbonate salt . . . ."

However, *Chazard* teaches calcium only as the counter-ion to the folinic acid, which is the active ingredient. *Chazard*, does not disclose that calcium has any activity of its own. The compositions of *Chazard* are directed to only potentiating or enhancing the effect of oxaliplatin:

> The present invention is directed to a dosage form suitable for oral administration to a mammal for the treatment of tumors, especially colorectal tumors, that exhibits a synergistically enhanced effect in combination with oxaliplatin. In particular, there is provided in accordance with the present invention a dosage form suitable for oral administration to a mammal having a tumor comprising an effective amount of each of tegafur, uracil, and folinic acid or a pharmaceutically acceptable salt thereof to a patient undergoing treatment with oxaliplatin, wherein said dosage form is a potentiator of oxaliplatin.

(¶ 0009.) In sum, folinic acid is administered specifically to potentiate 5-FU action and allow for oral administration of 5-

FU. *Chazard* is completely silent as to any protection against oxaliplatin neurotoxicity provided by calcium folinate.

Thus, *Chazard* does not teach a calcium salt other than calcium folinate, *i*.e., as a folinic acid source. Claim 6, from which claims 13-14 depend, explicitly requires oral administration of a calcium salt other than calcium folinate. Accordingly, *Chazard* provides no rationale for one of skill in the art to combine the teaching of Chazard with the teaching of *Lainé-Cessac*, to arrive at the claimed invention. The rejection provides no such rationale. For this reason alone, the rejection does not present a *prima facie* case for the obviousness of the claims as amended.

In addition, any combination of *Lainé-Cessac* and *Chazard* that results in the claimed method must necessarily include the injection of magnesium and calcium. However, such a method would destroy the operability of *Chazard*. Simply put, a method requiring an injection would 1) increase the cost of therapy and 2) removes the psychological benefits afforded a patient by taking an oral medication. Both of which are stated objects of the invention of *Chazard*.

However, a modification of references that destroys the operability of the references is not obvious. See, *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) (reversing the decision of obviousness on the ground that the proposed modification of the prior art would have rendered the claimed invention inoperable for its intended purpose). For this additional reason, the rejection fails to present a *prima facie* case for obviousness and withdrawal is requested.

As discussed in the Applicants' previous response (November 28, 2007), the claimed invention is also nonobvious because it solves a problem that the prior art did not recognize. This argument stands unrebutted by the present Office Action and is re-presented here for completeness.

Before the present Applicants' invention, it was believed that the neurotoxic effects of oxaliplatin appeared only during or immediately after infusion of the oxaliplatin. In other words, the late-onset of neurotoxic effects was not a concern. Consequently, and as borne out by the cited prior art itself, therapies for treating these neurotoxic effects focused exclusively on immediate treatment. *See, e.g., Lainé-Cessac*. However, this belief turned out to be mistaken. As Applicants explained in paragraph [0053] of the present specification, "[i]n some cases, it is found necessary to continue with the administration of Ca in order to reduce the risk of ***onset of neurological manifestations at a distance from the administration of oxaliplatin***." (Emphasis added.) In solving this problem with a combination of injectable and oral administration of calcium, Applicants' claimed invention thus produces unexpected results in treating the previously unappreciated late-onset neurological side effects of oxaliplatin.

Inventions based on application of known solutions to previously unknown problems have been held to be non-obvious and patentable. In *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923), the Supreme Court ruled that the first recognition of the existence of a problem is not obvious and involves discovery and invention. In *Eibel Process*, the patent in question was directed to an improvement in a standard paper making machine. In the machine, a stream of pulp stock flowed onto a moving wire cloth in order to drain water out of the stock over the 30 foot-length of the cloth. The prior art taught that increasing the speed of the wire cloth increased productivity, but at the same time, caused the defective paper with poor quality. The patentee's contribution was to increase the pitch of the wire cloth in order to use gravity to increase

the rate of flow of pulp on the wire cloth to equal the rate of flow of the wire cloth itself. The Supreme Court held thusly:

> It was the discovery of the source not before known and application of the remedy for which *Eibel* was entitled to be rewarded in his Patent. . . . We cannot agree with the Circuit Court of Appeals that the causal connection between the unequal speeds of the stock and the wire, and the disturbance and rippling of the stock, and between the latter and the defective quality of the paper in high speeds of the machine was so obvious that perception of it did not involve discovery which will support a patent.

Eibel Process, at 68.

Similarly, in *In re Nomiya*, 509 F.2d 566, 184 USPQ 607 (C.C.P.A. 1975), the Court of Customs and Patent Appeals (CCPA) held that the doctrine established by the Supreme Court in *Eibel Process* also applies when the inventor was the first to encounter or perceive a problem even though he uses known or obvious means of solving it. *Nomiya* dealt with an improvement in an insulated gate-type field effect transistor (IGFET) for use as a switching device in memory circuits having very low capacitance. The CCPA reasoned thusly:

> If, as appellants claim, there is no evidence of record that a person of ordinary skill in the art at the time of appellants' invention would have expected the problem in the IGFET to exist at all, it is not proper to conclude that the invention which solves this problem, which is claimed as an improvement of the device, would have been obvious to that hypothetical person of ordinary skill in the art. The significance of evidence that a problem was known in the art is, of course, that knowledge of a problem provides a reason or motivation for workers in the art to apply their skill to its solution. Logically, the instant situation is one step removed from the circumstances illustrated by *Eibel Process*

> *Co. v. Minnesota & Ontario Paper Co.* … where *the problem* of rippling in paper produced on Fourdrinier paper-making machines at high speed *was known*, but the source of the problem was not.

Nomiya, 509 F.2d at 572, 184 USPQ at 612-613.

For this additional reason, the rejection fails to present a *prima facie* case for obviousness. Accordingly, for all of the foregoing reasons, the reconsideration and withdrawal of the rejection is requested.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that she telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections which she might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: December 28, 2009

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